From Goals to Habits in Alcohol Dependence: Psychological and Computational Investigations

Dissertation

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Eidesstattliche Erklärung

Hiermit erkläre ich,

- dass ich die vorliegende Arbeit selbstständig und ohne unerlaubte Hilfe verfasst habe,
- dass ich die Dissertation an keiner anderen Universität eingereicht habe und keinen Doktorgrad in dem Promotionsfach Psychologie besitze und
- dass mir die Promotionsordnung der Mathematisch-Naturwissenschaftlichen Fakultät II vom 17.01.2005, zuletzt geändert am 13.02.2006, veröffentlicht im Amtlichen Mitteilungsblatt Nr. 34/2006 bekannt ist.

Berlin, November 2016, Miriam Sebold

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Abstract

Alcohol dependence (AD) manifests as a strong drive to consume alcohol despite serious adverse consequences. A popular theory in addiction research thus suggests that AD is characterized by a shift from goal-directed to habitual control, where actions are automatic and disentangled from outcomes. Evidence for this has mainly been drawn from experimental investigations in animals, with comparably little translation of these procedures to humans. Whereas these paradigms relate to behavioral psychology, the field of machine learning has recently advanced new experiments that allow the application of reinforcement learning algorithms to investigate a shift towards habits. Again, these tasks have yet not been applied to human AD. Moreover it remains unclear how experiments from these diverse fields relate to each other.

To fill this gap, this thesis investigates habitual at the expense of goal-directed control from distinct theoretical fields in AD patients. We adapted a Pavlovian-to-Instrumental transfer (PIT) procedure from the animal literature, which quantifies habits as cue-induced control over behavior *(Paper I)*. Then, we applied an experimental procedure inspired from machine learning (Two-Step task) that allows to investigate the balance between habitual and goal-directed control *(Paper II)*. Third, we examined the relationship between behavior across these paradigms *(Paper III)*. Last, we investigated whether the imbalance between habitual and goal-directed control was associated with alcohol consumption in non-pathological, social drinkers *(Paper IV)*.

We observed the following results:(1) AD was associated with increased cue-induced habits, as measured by the PIT task.(2) AD patients showed a selective shift away from goal-directed control in the Two-Step task. In line with these findings,(3) healthy controls who showed enhanced habits in the PIT task, demonstrated reductions in goal-directed control in the Two-Step task.(4) Alcohol consumption in non-pathological drinkers was not associated with an imbalance between habitual and goal-directed control in the Two-Step paradigm.

Our results add further evidence that AD is associated with a shift from goal-directed to habitual control, e.g. increased cue-induced control / reductions in goal-directed decision-making. In healthy controls, these phenomena were associated with each other, suggesting the involvement of similar mechanisms. As non-pathological alcohol intake was not associated with an imbalance between goal-directed and habitual control, this imbalance might arise over the course of AD rather than being a trait marker of alcohol intake.

Zusammenfassung

Alkoholabhängigkeit (AA) zeichnet sich durch einen starken Drang nach Alkoholkonsum trotz schwerwiegender negativer Folgen aus. Eine gängige Theorie aus der Suchtforschung besagt deshalb, dass AA mit einer Verlagerung von zielgerichteter zu habitueller Kontrolle einhergeht, durch welche Handlungen automatisiert ausgeführt werden und weitgehend unabhängig von ihren Folgen sind. Belege für diese Theorie stammen weitgehend aus experimentellen Untersuchungen an Tieren, welche nur unzureichend auf den Menschen übertragen wurden. Während diese Paradigmen dem Gebiet der Verhaltenspsychologie entstammen, hat das Fachgebiet des maschinellen Lernens kürzlich neue Experimente hervorgebracht, welche die Anwendung von Algorithmen des bestärkenden Lernens erlauben, um habituelle Kontrolle zu untersuchen. Auch diese Paradigmen fanden bisher keine Anwendung in der Untersuchung von Patienten, die an AA leiden. Zudem ist unklar, wie die Paradigmen aus den unterschiedlichen theoretischen Disziplinen miteinander assoziiert sind.

Um diese Lücke zu füllen, widmet sich diese Dissertation der Untersuchung von habituellem und zielgerichtetem Verhalten bei AA aus unterschiedlichen Perspektiven. Hierfür adaptierten wir zunächst ein Pawlowsch-Instrumentelles Transfer (PIT) Paradigma aus der Tierliteratur, durch welches habituelles Verhalten als reizgesteuerte Kontrolle quantifiziert wird *(Paper I)*. Anschließend nutzten wir eine Aufgabe (Two-Step), die aus dem maschinellen Lernen stammt und die Untersuchung der Balance von habitueller und zielgerichteter Kontrolle ermöglicht *(Paper II)*. Drittens untersuchten wir den Zusammenhang des Verhaltens ber beiden Paradigmen hinweg *(Paper III)*. Zuletzt untersuchten wir, ob jene Balance mit dem Alkoholkonsum in sozialen Trinkern - welche die Diagnose AA nicht erfüllen - assoziiert ist *(Paper IV)*.

Die folgenden Hauptergebnisse wurde gefunden:(1) AA war assoziert mit erhöhtem reizinduziertem habituellem Verhalten, gemessen mit der PIT Aufgabe.(2) AA Patienten zeigten selektive Verminderung im zielgerichteten Verhalten in der Two-Step Aufgabe.(3) Jene gesunden Probanden, die erhöhtes reizgesteuertes habituelles Verhalten in der PIT Aufgabe zeigten, zeichneten sich durch verminderte zielgerichtete Kontrolle in der Two-Step Aufgabe aus.(4) Alkoholkonsum von sozialen nicht-pathologischen Trinkern war nicht assoziiert mit dem Ungleichgewicht zwischen habituellem und zielgerichtetem Verhalten in der Two-Step Aufgabe.

Diese Ergebnisse liefern weitere Hinweise auf eine Verlagerung von zielgerichteter zu habitueller Kontrolle bei AA (verstärktes reizgesteuertes habituelles Verhalten/

verminderte zielgerichtete Entscheidungsfähigkeit). Bei gesunden Probanden waren diese Phänomene miteinander assoziiert, was darauf rückschließen lässt, dass sie ähnliche kognitive Mechanismen rekrutieren. Der Nullbefund bzgl. Alkoholkonsum bei sozialen Trinkern und dem Ungleichgewicht zwischen habitueller und zielgerichteter Entscheidungskontrolle weist darauf hin, dass eine Verlagerung von zielgerichteter zu habitueller Kontrolle erst im Verlauf der AA entsteht und kein Korrelat von Alkoholkonsum per se darstellt.

List of Papers

This thesis is based on the following original papers

Paper I

Garbusow, M., Schad, D.J., Sommer, C., Jünger, E., **Sebold, M.**, Friedel, E., Wendt, J., Kathmann, N., Schlagenhauf, F., Zimmermann, U.S., Heinz, A., Huys, Q.J.M., Rapp, M.A., (2014), Pavlovian-to-instrumental transfer in alcohol dependence: a pilot study.*Neuropsychobiology* 70 (2), 111-21.

Paper II

Sebold, M., Deserno, L., Nebe, S., Schad, D.J., Garbusow, M., Hägele, C., Keller,J., Jünger, E., Kathmann, N., Smolka, M., Rapp, M.A., Schlagenhauf, F., Heinz, A., Huys, Q.J.M., (2014), Model-based and model-free decisions in alcohol dependence. *Neuropsychobiology* 70 (2), 122-31.

Paper III

Sebold, M., Schad, D.J., Nebe, S., Garbusow, M., Jünger, E., Kroemer, N.B., Kathmann, N., Zimmermann, U.S., Smolka, M.N., Rapp, M.A., Heinz, A., Huys, Q.J.M, (2016), Don't think, just feel the music: Individuals with strong Pavlovian-to-instrumental transfer effects rely less on model-based reinforcement learning. *Journal of cognitive neuroscience* 28 (7), 985-995.

Paper IV

Nebe, S., Kroemer, N.B., Schad, D.J. Bernhardt, N., **Sebold, M.**, Müller, D.K., Scholl, L., Kuitunen-Paul, S., Heinz, A., Rapp, M.A., Huys, Q.J.M, Smolka, M.N., (2017) No association of goal-directed and habitual control with alcohol consumption in young adults. *Addiction biology*, Epub ahead of print, doi: 10.1111/adb.12490

List of minor Papers

In this dissertation, I will also refer to the following papers, I was involved in. However, for this dissertation, these papers are of minor interest.

Paper V

Garbusow, M., Schad, D.J., **Sebold, M.**, Friedel, E., Bernhardt, N., Koch, S.P., Steinacher, B., Kathmann, N., Geurts, D.E.M., Sommer, C., Müller, D.K., Nebe, S., Paul, S., Wittchen, H-U., Zimmermann, U.S., Walter, H., Smolka, M.N., Sterzer, P., Rapp, M.A., Huys, Q.J.M., Schlagenhauf, F., Heinz, A., (2015), Pavlovian-to-instrumental transfer effects in the nucleus accumbens relate to relapse in alcohol dependence. *Addiction biology,21:719-731*

Paper VI

Schad, D.J., Jünger, E., **Sebold, M.**, Garbusow, M., Bernhardt, N., Javadi, A., Zimmermann, U.S, Smolka, M.N, Heinz, A., Rapp, M.A., Huys, Q.J.M., (2014), Processing speed enhances model-based over model-free reinforcement learning in the presence of high working memory functioning. *Frontiers in psychology,5:1450.*

Paper VII

Schad, D.J., Garbusow, M., Friedel, E., Sommer, C., **Sebold, M.**, Hägele, C., Bernhardt, N., Nebe, S., Kuitunen-Paul, S., Liu, S., Eichmann, U., Beck, A., Wittchen, H-U., Walter, H., Sterzer, P., Zimmermann, U.S., Smolka, M., Schlagenhauf, F., Huys, Q.J.M., Heinz, A., Rapp M.A. (under revision), Neural correlates of instrumental responding in the context of alcohol-related cues index disorder severity and relapse risk.

List of Abbreviations and Glossary

AD \AA:	Alcohol dependence \Alkoholabhängigkeit (in german)
COMT:	Catechol-O-methyl transferase
CS:	Conditioned stimulus: A stimulus, which predicts the occurrence of a reward
Devaluation Paradigm:	Experimental approach to investigate goal-directed vs. habitual control in rodents. Animals learn to associate a cue (e.g. light) with a response (e.g. lever press) to receive a rewarding outcome (e.g. food). The outcome is then devalued (e.g. feeding to satiety). Only if the response is goal-directed, the animal stops responding when confronted with the cue.
DSST:	Digit symbol substitution test: test to assesses fluid intelligence/ cognitive speed introduced by Wechsler (1981).
Incentive Salience:	A phenomenon, which indicates the motivating properties of a reward-related stimulus. The cue itself elicits appetitive responses/ approach behavior.
Instrumental Conditioning:	Behavioral learning procedure in which the strength of a response is modified by its outcome (reward or punishment).
mPFC:	Medial prefrontal cortex
NcACC:	Nucleus accumbens
PIT:	Pavlovian-to-Instrumental Transfer: A phenomenon, which indicates that cues, which have been associated with positive outcomes, increase instrumental responding for the same outcome (specific PIT) or another positive outcome (general PIT).
Reinforcement Learning:	Area of machine learning, where theory-driven algorithms model how systems can learn to choose actions that maximize reward and minimize punishment.
RPE:	Reward prediction error: the difference between expected and experienced reward is used to update future expectations and to guide action selection.
RT:	Reaction times
SORC Model	Model for conceptualizing a clinical problem: S - Stimulus, that elicits problematic behavior. O - Organismic variable related to the problematic behavior. R - Response or problematic behavior. C - Consequence of the problematic behavior.
SUD:	Substance use disorder
US:	Unconditioned stimulus: A stimulus, which is itself pleasurable and rewarding prior to Pavlovian conditioning.
VS:	Ventral striatum

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Why is it possible to want, what is not expected to be liked, nor remembered to be liked and not actually liked when obtained?

(Berridge, 2012)

1 Introduction

Habits are automatized behaviors that can be triggered by environmental cues (Dickinson, 1985). Habits bring tremendous benefits in our everyday lives, as they allow to efficiently perform action routines, while requiring minimal cognitive effort (Gillan et al., 2016). Without our ability to execute habits we were unable to lace our shoes in the morning while concurrently discussing the dinner plans with our partner. However, the downside of habits is, that these actions are rather inflexible. This is why the shoe lacing becomes difficult when one hand is injured. This condition forces us to suppress automatic action tendencies and to apply cognitive control to each step of the shoe lacing technique just as when we learnt this procedure for the very first time. In situations like these, we need to override our habits by applying more deliberative and flexible goal-directed behavior. The ability to override habits has been suggested to be impaired in alcohol dependence (AD) (Everitt and Robbins, 2005), where maladaptive behavior is characterized by resistance to change. Indeed, AD patients continue to drink alcohol despite serious adverse consequences such as social isolation, unemployment or alcohol related delinquency (Volkow and Li, 2004) and even if the consumption causes negative emotional responses or anhedonia (Berridge, 2012). These habits can interfere with goal-directed intentions (Dolan and Dayan, 2013), for example, when patients wish to abstain from alcohol. Habits at the expense of goal-directed control might thus contribute to the chronicity of the disorder, with relapse rates up to 85% (Boothby and Doering, 2005). Therefore, the identification of the biological and cognitive mechanisms of habit formation in AD is a promising target for the development of new pharmacological and psychotherapeutic interventions.

2
Theoretical Background

Initial alcohol intake is mostly associated with hedonic, pleasurable effects (Cunnigham et al., 1993). As actions that result in reward become more likely to reoccur (Thorndike, 1898), alcohol consumption can be seen as conditioned response, acquired through action-outcome associations. However, AD is defined by a persistence of this acquired response, even when alcohol consumption has lost its reinforcing effects. This is reminiscent of habits, where behavior is strongly automatized and insensitive to its associated outcome (Dickinson, 1985; Dolan and Dayan, 2013). Habitual alcohol intake in AD has been argued to rely on an imbalance between two decision-making systems (Everitt and Robbins, 2005). There are different theoretical formulations on how these decision-making systems operate in humans and a distinction between two theories was framed, that I will henceforth refer to as *psychological* and *computational* approach. The psychological framework refers to phenomena and paradigms that are grounded in the animal literature and fall within the field of behavioral psychology. Within this field, conventional statistical models are applied that allow descriptive characterization of habit phenomena. The computational framework, on the other hand refers to phenomena and paradigms that derive from machine learning. Within this field, generative, algorithmic models of behavior are applied and provide mechanistic accounts on the underlying computations of habit phenomena (Stephan et al., 2015). Importantly, both multiple-control frameworks consistently implicate that AD is accompanied by a shift from goal-directed to habitual control (Lucantonio et al., 2014; Huys et al., 2016; Robbins and Everitt, 1999). In humans, there are comparably little investigations that test this theoretical assumption. One major goal of this dissertation was therefore to test whether AD is indeed accompanied by a dominant habit system at the expense of a reflective goal-directed system. We tested this by using two different paradigms that relate to the psychological and computational framework, respectively. Furthermore, a second goal was to test, whether these two dual-system accounts are indeed related. Moreover, as there is evidence that a shift towards habit formation in AD does not only reflect a consequence but also a cause of chronic alcohol intake (Redish et al., 2008), a third aim was to test whether alcohol consumption in social drinkers, who had not been exposed to long-term alcohol intake was associated with an imbalance between habitual and goal-directed control.

2.1 Goals and habits: a psychological perspective

According to a psychological multiple-control account, actions can be either automatically elicited by external cues (habitual) or guided by the anticipated consequences of an action (goal-directed). Crucially, a shift from goal-directed to habitual control in AD might rely on two mechanisms: Enhanced cue-triggered responses and/or disruption of goal-directed behavior through inadequate outcome anticipation.

2.1.1 Cue-triggered responses in AD

In AD, alcohol cues cause strong physiological responses (Beck et al., 2012; Carter and Tiffany, 1999), which are related to self-reports of craving (Wrase et al., 2007; Hogarth et al., 2010) and may cause automatic approach behavior towards these cues (Barkby et al., 2012; Wiers et al., 2011). These cue-induced motivations in AD likely reflect conditioned appetitive responses, which are a result of Pavlovian reward learning. Evidence for this comes from microdialysis studies in animals, which demonstrate that after chronic alcohol intake, alcohol cues lead to increased dopamine release in the nucleus accumbens (NcAcc) (Katner et al., 1996). Likewise, after stimulus-stimulus learning, non-drug related, reward predictive stimuli lead to increased dopaminergic transmission in the midbrain (Schultz et al., 1997). Alcohol itself increases dopamine concentration in the midbrain and the NcAcc, just as other natural rewards like food or sex (Kelley and Berridge, 2002; Boileau et al., 2003). Thus, in AD alcohol associated cues may become conditioned stimuli (CSs), which indicate the occurrence of a nearby reinforcer (unconditioned stimuli or UCs) via dopaminergic reward prediction error (RPE) signals. The incentive salience theory of addiction therefore suggests, that drugs of abuse including alcohol produce incremental neuroadaptations in the dopaminergic system which cause hypersensitivity to alcohol associated stimuli, making them attractive, "wanted" stimuli (Robinson and Berridge, 1993).

2.1.2 Pavlovian-to-instrumental Transfer

Alcohol related cues not only elicit arousal and approach responses in AD patients but can also gain control over behavior. Indeed, it was shown that alcohol cues may foster alcohol consumption and craving in humans (Litt et al., 2000; McCusker and Brown, 1990). In animals, alcohol-cues have been further shown to contribute to relapse by reinstating drug-seeking behavior (Katner et al., 1999; Crombag et al., 2008; Glasner et al., 2005). Thus, Pavlovian cues can exert control over previously instrumentally acquired responses, a behavioral phenomenon termed Pavlovian-to-instrumental Transfer (PIT). The PIT phenomenon has been descibed in two distinct versions: outcome-general and outcome-specific (Dolan and Dayan, 2013; Talmi et al., 2008; Corbit and Balleine, 2005). In specific PIT, cues are associated with a specific reward and enhance instrumental actions for the same reward (e.g. alcohol associated stimuli increase responding for alcohol). In general PIT, however, cues that are related to one reward enhance responses for a different reward (e.g. alcohol associated stimuli enhance instrumental responding for food). At least in animals, chronic alcohol intake enhances both versions of PIT: Rats that were sensitized to alcohol show increased instrumental responding for alcohol when confronted with alcohol cues (Krank, 2003; Glasner et al., 2005; Corbit and Janak, 2007; Krank et al., 2008; Milton et al., 2012; Lamb et al., 2016), an exemplification for specific PIT effects. Moreover, chronic alcohol intake enhances the extent to which alcohol cues influence responding for alternative rewards (e.g. food; Glasner et al. 2005; Corbit and Janak 2007), which can be seen as a conceptualization of general PIT. As chronic drug intake, such as alcohol also enhance the extent to which food-cues control food-related responses (Ostlund et al., 2014), it was concluded that drug exposure causes alterations in general reward and decision mechanisms.

Although several studies have sucessfully developped experimental paradigms to study PIT effects in humans (Prévost et al., 2012; Bray et al., 2008; Trick et al., 2011; Talmi et al., 2008), comparably little work has yet been conducted in the clinical field. In smokers, Hogarth et al. (2007) and Hogarth and Chase (2011) demonstrated that the presence of cigarette cues increases responses for cigarettes. Moreover in a subclinical cohort, social drinkers showed increased responding for alcohol when alcohol cues were present (Martinovic et al., 2014; Van Dyke and Fillmore, 2015). So far, no study has investigated whether alcohol cues or other reward-related stimuli increase instrumental responding in AD subjects. Such investigation could shed light on habits in terms of incentive salience attribution and its impact on action selection in human AD.

2.1.3 Disruption of goal-directed control in AD

Besides the above mentioned phenomena, which describe that Pavlovian stimuli may trigger maladaptive responses and exert control over behavior, habits in AD have been further mapped to a disruption of goal-directed control. Goal-directed control typically reflects two mental representations, (a) the knowledge of the outcome that an action produces and (b) the current motivation for this outcome (Dickinson and Balleine, 1994). Thus, chronic alcohol intake might elicit inadequate mental representation of action-outcome contingencies and/or actions that are incongruent with the need and desire for the outcome. Although the nature of the underlying processes remains unclear, in animals it was demonstrated, that repeated ethanol exposure leads to a disruption in goal-directed control. Evidence for this mainly derives from devaluation paradigms, in which the execution of a response, that has previously led to reward, is tested after the reward has been devalued for instance by pairing it with sickness. Dickinson and Balleine (2002) demonstrated that behavior reinforced by alcohol was more resistant to devaluation than behavior that had been reinforced by food. Consistently, after chronic alcohol consumption, rats become insensitive to devaluation of alcohol (Lopez et al., 2014) and food (Corbit et al., 2012). Alcohol exposure thus might have a special propensity to establish automatic actions that are insensitive to the value of the outcome to which they will lead. The study by Dickinson and Balleine (2002) was translated to humans, as Hogarth et al. (2012a) demonstrated that alcohol intake in healthy subjects produces behavior that is resistant to outcome devaluation. However, this relates merely to acute alcohol effects. Despite the growing body of literature in animals that investigate the effects of chronic alcohol exposure on goal-directed control, in humans, so far there are a limited number of studies investigating this link. Crucially, in patients, devaluation studies, that test alcohol consumption after alcohol devaluation are unethical and the use of non-alcohol digestive rewards in human devaluation studies limits the sample to individuals who enjoy the specific food or drink options (Valentin et al., 2007; McKim et al., 2016b). So far, only one study investigated goal-directed decision-making in human AD subjects by using a task with abstract stimuli, that was inspired by devaluation paradigms from the animal literature. This study showed that AD subjects displayed disruptions in goal-directed decision-making (Sjoerds et al., 2013). Just recently, by using similar tasks, these findings have been translated to humans suffering from other substance use disorders (SUD) (McKim et al., 2016a), including cocaine (Ersche et al., 2016).

Taken together, there are several processes that potentially underly the shift from goal-directed to habitual control in AD. Crucially, the three above mentioned phenomena (Cue-triggered responses, PIT, devaluation sensitivity) that indicate this shift are related to each other. For instance rats, that show a propensity to attribute incentive salience to cues are resistant to devaluation (Morrison et al., 2015) and those rats who show strong PIT effects are less sensitive to outcome devaluation (Barker et al., 2014). Moreover, humans who demonstrate strong incentive salience attribution show enhanced general PIT effects (Garofalo and di Pellegrino, 2015). The relationship between these phenomena render a summary under the umbrella term *a psychological account of habits and goal-directed control* plausible.

2.2 Goals and habits: a computational perspective

Beside the psychological account of habitual and goal-directed decision-making (see 2.1), the theoretical formulation of a multiple-control system has recently been applied to the field of reinforcement learning, an area of machine learning. In this field, theory-driven mathematical algorithms model how systems (including humans) can learn to choose actions that maximize reward and minimize punishment (Sutton, 1998). These algorithms can then be used to simulate and reproduce human decision-making. Crucially, These models were particularly powerful in characterizing maladaptive decision-making processes across several psychiatric disorders (Maia, 2009; Redish et al., 2007; Maia and Frank, 2011; Huys et al., 2016).

2.2.1 Model-based and model-free control

Two ends of a spectrum of these mathematical algorithms instantiate model-based and model-free control, the computational dual-control framework which mirrors the psychological distinction of goal-directed and habitual decision-making (Doya et al., 2002; Daw et al., 2005; Niv et al., 2006). Whereas the model-free system simply learns which actions are followed by reward, it is also rigid and inflexible, just like the psychological instantiation of habitual control. The model-based system, on the other hand, uses knowledge to prospectively reason about the value of actions, which makes it sensitive to sudden outcome changes, a hallmark of goal-directed control (Dolan and Dayan, 2013). More precisely, model-free algorithms compute action-values according to past and therefore "cached" rewards but neglects environmental structures, such as where a path in a maze leads. Model-based algorithms, on the other hand, use these environmental structures and therefore enable flexible and adaptive decision-making. In humans, this dual-control framework was experimentally conceptualized by using multi-choice Markov decision tasks (Glascher et al., 2010; Doll et al., 2015), which allow to quantify the balance between model-free and model-based control on a trial by trial basis, for instance in the so-called Two-Step task (Daw et al., 2011). By using this task, Daw et al. (2011) and Glascher et al. (2010) demonstrated that human decision-making show imprints of both systems, although there is substantial interindividual variability in the balance between them. As the psychological dual-control framework of addiction suggests a shift from goal-directed to habitual behavior, a theoretical translation into the computational dual-control counterpart proposes a predominance of model-free at the expense of model-based decision-making in addiction (Dolan and Dayan, 2013). One advantage of reinforcement learning models is that they can capture several aspects of neural activity even though they are not grounded in biophysiology. One prominent example is that temporal-difference learning, a special case of model-free reinforcement learning, correctly predicts a dopaminergic RPE signal (Eshel et al., 2015; Montague et al., 1996; Schultz et al., 1997; Takahashi et al., 2016). Indeed, these RPE's underly reward-seeking behavior in healthy subjects (Pessiglione et al., 2006) and correlate with craving in AD (Deserno et al., 2015). Several theoretical accounts have therefore suggested that alcohol-related dopamine release augments the selection of a model-free decision-making system that overselects actions leading to alcohol receipt (Redish, 2004; Dayan, 2009). This decision-making bias might promote general inflexible responding beyond the domain of alcohol seeking, such that action-selection is ultimately biased towards model-free learning (Lawrence et al., 2009; Park et al., 2010). However, until now, a predominance of the model-free at the expense of the model-based system in human AD subjects has not been tested.

2.3 Psychological and computational perspective: Theoretical and experimental integrations

Although the psychological and the computational dual-control framework have been described as theoretical counterparts, so far only few studies have experimentally tested this association. The investigation of factors that shift behavioral dominance from one system to the other suggest that the same cognitive and emotional processes are involved across both dual-system accounts. For instance, extensive training was demonstrated to shift model-based to model-free decision-making (Keramati et al., 2011; Wunderlich et al., 2012) and goal-directed to habitual responding (Dickinson et al., 1983; Holland, 2004). Likewise, stress prompted habits in devaluation tasks (Schwabe and Wolf, 2009; Schwabe et al., 2010) and impaired model-based control (Radenbach et al., 2015; Otto et al., 2013b). Higher cognitive functions (see *Paper VI*) such as working memory were also associated with model-based control (Otto et al., 2013a,b) and correlated with the individual ability to retain goal-directed behavior (Collins and Frank, 2012). Recently, Friedel et al. (2014) and Gillan et al. (2015) showed that individual differences in model-based learning as assessed by the Two-Step Task were directly associated with participants' devaluation sensitivity, thus demonstrating that the computational and the psychological dual-control constructs are indeed related. The psychological multiple control framework of habits and goal-directed behavior includes Pavlovian influences on choice behavior as in the PIT phenomenon (see 2.1.2), and indeed, several theoretical papers have mapped the model-based/ model-free dichotomy on PIT effects (Dolan and Dayan, 2013; Dayan and Berridge, 2014). Specific PIT effects have been suggested to stem from model-based computations as it requires access to the sensory identity of the outcome paired with the Pavlovian stimulus. General PIT, on the other side has been termed as model-free, because the invigoration of the response by the Pavlovian stimulus does not require a mental model of the outcome (Clark et al., 2012). However, this has only been on theoretical grounds and so far it has not been experimentally tested whether individual variation in the balance between model-free and model-based is associated with PIT effects.

2.4 From goals to habits - cause or consequence of chronic alcohol intake?

Alterations in the decision process in AD patients could, on the one hand, be a consequence of chronic alcohol intake or, on the other hand, reflect a preexisting trait marker, indexing the vulnerability for developing AD. In humans, studies in subjects who are at risk for the development of AD support the latter hypothesis. One risk factor for the development of AD is trait impulsivity, which predicts alcohol intake in humans and animals (Granö et al., 2004; Belin et al., 2008) . High impulsivity is associated with several phenomena that reflect a transition from goal-directed to habitual control: high impulsive individuals show decreased goal-directed behavior in devaluation tasks (Hogarth et al., 2012b) and increased general PIT effects (Garofalo and di Pellegrino, 2015). Moreover, impulsive traits correlated with disruptions in model-based control (Gillan et al., 2016; Reiter et al., 2016).
Variability of dopamine genes are a further risk factor for the development of AD: For instance the genetic polymorphisms of catechol-O-methyltransferase (COMT) was associated with AD (Kreek et al., 2005) as well as the balance between model-based and model-free control (Doll et al., 2016). Further support for the notion that interindividual variability in habitual at the expense of goal-directed control may be a predictor for the development of AD come from animal studies. For instance, Flagel et al. (2011, 2009, 2014) have shown, that animals, who show increased incentive salience attribution to formerly neutral cues have a higher propensity to acquire addictive-like behavior. Moreover, Barker et al. (2012, 2014) demonstrated that high general PIT effects precedes excessive alcohol intake, which is insensitive to devaluation and extinction. Crucially in theses studies, PIT effects were tested before alcohol exposure, suggesting that habitual at the expense of goal-directed responding indeed is an endophenotype for addiction vulnerability. So far, in humans it has yet not been investigated whether a bias towards habitual at the expense of goal-directed control is a preexisting cognitive vulnerability marker for the development of AD.

3 Summary and Research Questions

As outlined in the previous chapter, AD is assumed to be associated with habitual responding at the expense of goal-directed control. This assumption can be incorporated in two dual control frameworks - a psychological (see 2.1) and a computational (see 2.2). The psychological dual control theory assumes that chronic alcohol intake shifts action-selection from a mode when it is driven by internal representations of needs and goals to a mode where it is automatically executed through external cues (see 2.1.1). One phenomenon that captures this rather automatic execution of a previously acquired response by environmental cues is the PIT effect (see 2.1.2), which has been widely tested in animals, but so far not in human AD subjects. Equivalent to the psychological dual-framework, the computational account assumes that chronic alcohol intake shifts action selection from a system where action-values are computed based on a model of the environment (model-based) to a mode where these computations are merely driven, by "stamped-in" and therefore cached reward values (model-free, see 2.2.1). This framework has been demonstrated to capture neural and behavioral features of decision-making in animals and healthy human subjects, but so far it has not been applied to human AD.

The clinical implications that both dual-framework accounts make are the same, namely that action-selection in AD is inflexible and rigid. Indeed, there are strong theoretical assumptions that both dual-control frameworks describe the same cognitive phenomenon from different perspectives and the terminologies "model-free" vs. "model-based" control are meanwhile used almost synonymous with the terms "habitual" vs "goal-directed. However, to date, it remains rather unclear whether these dual-control frameworks are indeed related and how experimental paradigms, that are assumed to instantiate these concepts are associated with each other (see 2.3). There is evidence, that a bias in the decision-making process towards habitual, model-free decisions is not merely a consequence of but probably a cause for chronic alcohol intake (see 2.4). If this were to be the case, this decision-making bias would be associated with alcohol intake in a subclinical sample. Here, I argue that the investigation of habits in AD might benefit from the translation of theoretically grounded experimental procedures that have been proven to depict habitual choice behavior in animals. Moreover, experimental procedures that enable to investigate choice behavior by mathematical algorithms might further shed light on the precise computations that underly habits in human AD. Specifically, the present dissertation aimed to use two paradigms to address the following questions:

1. Do Pavlovian stimuli exert greater control over instrumental decision-making (PIT effect) in AD patients compared to healthy controls? Do these group effects depend on the nature of the Pavlovian stimulus, e.g. whether they are alcohol-related or not?

2. Do human AD patients show an over-reliance of the model-free at the expense of a model-based decision-making system?

3. How does model-free vs. model-based and habitual vs. goal-directed control relate to each other? In particular, is the individual variation in PIT effects associated with the balance between model-free/ model-based control?

4. Is model-free at the expense of model-based decision-making a cause or a consequence of AD? In particular, is alcohol consumption in young men associated with the balance between model-based an model-free control?

This dissertation is publication oriented and the Questions 1,2,3 and 4 relate to the papers I,II,III and IV respectively. The following chapters will describe the precise methods on how these questions were addressed and the results of these investigations.

4
Methods

4.1 Samples

The data of all four studies was collected for a bicentric study hosted at Charité Universitätsmedizin zu Berlin and Technische Universität Dresden, Germany. The study examines learning and habitization in AD (*the LeAD study*, funded by the German Research Society (*DFG*)) and is headed by Prof. Dr. Dr. Heinz and Prof Dr. Wittchen. *Papers I* and *II* are based on data from the piloting phase of the *LeAD* study and included AD patients according to DSM-IV criteria. Crucially, at the time of study participation, all patients were abstinent from alcohol for at least three consecutive days and at most for 21 days. All healthy control subjects for *Paper I* and *II* were carefully matched to the patients according to demographic characteristics such as age, education and gender. *Paper III* and *Paper IV* are based on data of the core study of the *LeAD* study. *Paper III* focused on analyzing two healthy cohorts differing on their demographic characteristics. The young sample, which served as a replication sample for *Paper III* was also used for *Paper IV*. All papers were generated at different times and for each paper we included all available data. Therefore sample sizes differ between papers, albeit they include partially overlapping subjects.

4.2 Paradigms

The Lead study applies two distinct paradigms that allow to investigate habitual vs. goal-directed control from the psychological and computational perspective, respectively (see 2.1 and 2.2). In *Paper I*, we developed a PIT Task (Fig 1) whereas in *Paper II* and *IV* we used the Two-Step Task (Fig 2), which allows to investigate model-free and model-based control on a trial-by-trial basis. In *Paper III* we used behavioral choice patterns from both tasks in order to investigate how both cognitive mechanisms are related (see 1.3).

4.2.1 PIT Task

This task includes three critical phases:
A.) The instrumental training (Fig 1A), where subjects learn to respond to go-stimuli.
B.) The Pavlovian conditioning (Fig 1B), where subjects learn to associate neutral stimuli (CSs) to certain outcomes (USs).
C.) The PIT part (Fig 1C), where subjects are asked to perform the previously acquired instrumental response (A) in the presence of the Pavlovian stimuli (CSs from B). Performance during this part was of major interest for *Paper I* and *III*. In this part of the task, fractal background stimuli from part B were occasionally replaced with alcoholic/water images (not shown here, but additionally analyzed in *Paper 1*).

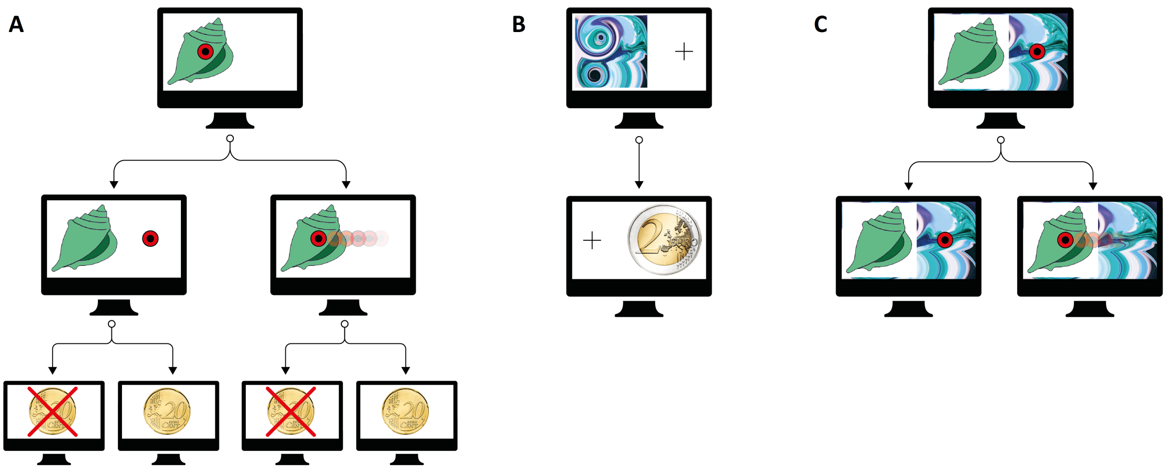

Figure 1: **The PIT Paradigm**
(A) Instrumental Training Subjects were instructed to collect shells by repeated button presses, after which they received probabilistic feedback. Collection of "Go-shells" was monetarily rewarded in 80% but punished in 20% of all trials and vice versa if not collected. Collection of "No-Go shells" was punished in 80% and rewarded in 20% of all trials and vice versa if not collected. Subjects performed a maximum of 120 trials. **(B) Pavlovian Conditioning** At each trial, subjects saw a fractal stimulus accompanied by the sound of a tone (compound CS). After a delay, a coin stimulus (US) was presented. Subjects were instructed to be attentive on the CS-US pairings. CS-US associations consisted of two CS paired with images of +2/+1 EUR coins, one CS paired with 0 EUR and two CS paired with -1/-2 EUR. Subjects completed 80 trials. **(C) PIT Part** Each trial consisted of the presentation of one of the previously learned shells (from A) superimposed on the fractals (from B). Subjects were instructed to perform the instrumental task again (collect "Go-shells" but leave "No-go shells"). No feedback was presented, but subjects were instructed that their choices would influence their final monetary outcome. Subjects completed 90 trials with fractals in the background.

4.2.2 Two-Step Task

This task consisted of 201 trials, each trial requiring two choices (Fig 2A). On each trial, subjects had to perform an initial choice (gray stimuli). This choice then led to one of two 2nd stage options (either green or yellow), where again one stimulus had to be selected. The transition from first stage choices to the specific 2nd stage was probabilistic: whereas one option on the first stage led frequently to the green 2nd stage option (70%) but rarely to the yellow 2nd stage option (30%), the other first stage choice was associated with frequent yellow 2nd stage visits (70%) but rare green 2nd stage visits (30%). After the 2nd stage choice, subjects were either monetarily rewarded or not. All four second-stage payoff probabilities changed slowly over time.

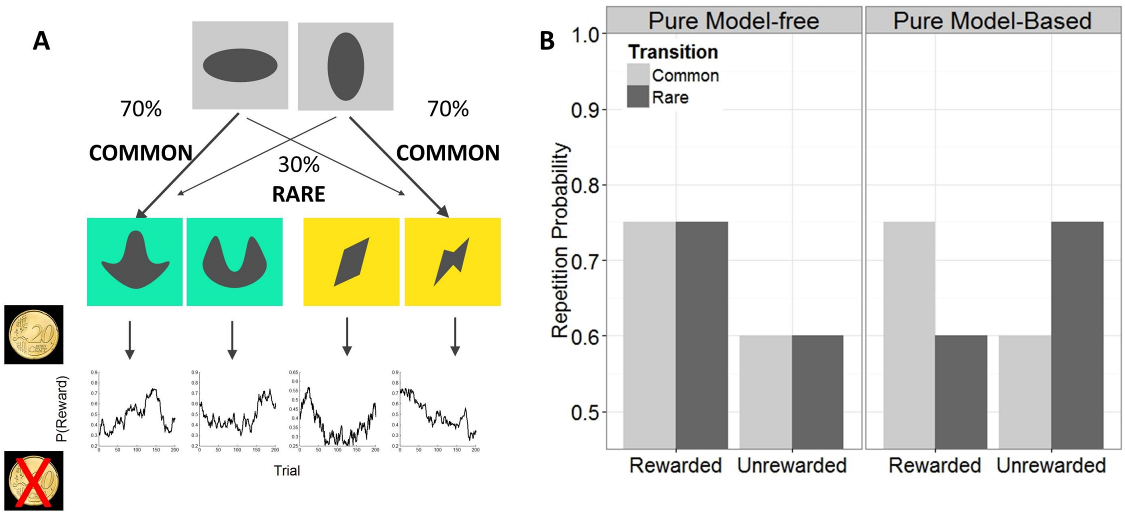

Figure 2: **The Two-Step Task**
(A) Trial Configuration (B) Model-based vs. model-free predictions Choices observed at first stage give inference on model-based vs. model-free control strategies. Model-free decisions do not consider transition frequencies: Actions resulting in immediate reward have higher probability to be repeated than actions which did not end up being rewarded, independent of whether the first stage choice resulted in a common or a rare second stage option. Thus, model-free decisions predict a main effect of reward on the next first stage choice. Only model-based decisions take transition probabilities into account. Here, the subject knows that reward omission after rare transitions actually suggest that the first stage choice should be repeated to increase the chance of getting to the opposing second stage stimulus pair. Thus, model-based decisions predict an interaction between reward and transition on next first stage choices.

5 Overview of publications

5.1 Paper I

Garbusow, M., Schad, D. J., Sommer, C., Jnger, E., **Sebold, M.**, Friedel, E., Wendt, J., Kathmann, N., Schlagenhauf, F., Zimmermann, U. S., Heinz, A., Huys, Q. J., Rapp, M. A., 2014. Pavlovian-to-instrumental transfer in alcohol dependence: a pilot study.*Neuropsychobiology* 70 (2), 111-121.

The overarching aim of *Paper I* was to investigate whether PIT effects are involved in AD. To this end, we implemented a PIT paradigm that mirrors previous experimental manipulations from animal studies and compared task performance between detoxified AD subjects and healthy controls.

Theoretical background In animals, chronic alcohol intake increases the extent to which reward-related stimuli exert control over choice behavior (Corbit and Janak, 2007; Ostlund et al., 2014; Glasner et al., 2005; Ostlund et al., 2014). This PIT phenomenon is considered to underly cue-induced craving in AD and promote relapse after detoxification (Barker et al., 2012; Lamb et al., 2016). However, in humans it has yet not been tested if PIT effects were associated with AD.

Hypotheses We adapted a recent experiment to study PIT effects in humans (Geurts et al., 2013; Huys et al., 2011), which allows to investigate the effects that alcohol and other reward-related cues have on instrumental behavior (Fig 1C for PIT with other reward-related cues). Based on the above mentioned findings, we hypothesized that patients with AD show stronger PIT effects both for stimuli predicting monetary outcomes and alcohol-related pictures.

Major findings As hypothesized and in line with animal models (Ostlund et al., 2014), AD patients compared to healthy controls tended to show increased PIT effects towards cues that had previously been reinforced with non-alcoholic reward (money). Alcohol-associated stimuli also exerted increased control over instrumental choice behavior in AD patients compared to healthy controls. However, in the presence of alcohol-associated stimuli, this effect was driven by avoidance rather than approach behavior. This effect in AD might reflect some sort of goal-directed control as consequence of cognitive reappraisal of alcohol-associated cues during detoxification.

5.2 Paper II

Sebold, M., Deserno, L., Nebe, S., Schad, D. J., Garbusow, M., Hagele, C., Keller,J., Junger, E., Kathmann, N., Smolka, M., Rapp, M. A., Schlagenhauf, F., Heinz, A., Huys, Q. J., 2014. Model-based and model-free decisions in alcohol dependence. *Neuropsychobiology* 70 (2), 122-131.

Paper II aimed to investigate whether AD is associated with habitual responding at the expense of goal-directed control. A main goal was to investigate this shift from a computational perspective (see 2.2), which equates habits with model-free and goal-directed with model-based control.

Theoretical background Chronic alcohol exposure may foster automatic actions that are insensitive to sudden value changes (Dickinson et al., 2000). This is reminiscent of model-free algorithms, where action-values are only slowly updated (Huys et al., 2016). Likewise, chronic alcohol may impair complex and flexible decision-making (Park et al., 2010; Lawrence et al., 2009), which can be computationally modelled by model-based algorithms that take complex action-outcome contingencies into account. However, to date a shift from model-based to model-free control in human AD has only been made on theoretical grounds and not yet been tested.

Hypotheses By using the Two-Step task, which allows to investigate the individual balance between model-free and model-based control, we tested whether there is a shift from model-based to model-free control in AD. Particularly, we expected AD patients compared to healthy controls to show increased model-free, habitual responding but reduced goal-directed, model-based action-selection.

Major findings Contrary to our prediction, AD patients did not show increased model-free control. However, in line with our hypothesis, we found a reduction of model-based control in AD. This alteration in the patient group was associated with a lack of behavioral adjustment after non-rewards, which is line with studies demonstrating impairments of adaptive decision-making after losses in AD (Lawrence et al., 2009). Crucially, model-based impairments in the patient group were attenuated when adjusting for general cognitive capacities, suggesting that model-based control relies on higher cognitive functions.

5.3 Paper III

Sebold, M., Schad, D. J., Nebe, S., Garbusow, M., Jnger, E., Kroemer, N. B., Kathmann, N., Zimmermann, U. S., Smolka, M. N., Rapp, M. A., Heinz, A., Huys, Q.J.M, 2016. Don't think, just feel the music: Individuals with strong Pavlovian-to-Instrumental Transfer effects rely less on model-based reinforcement learning. *Journal of cognitive neuroscience* 28 (7), 985-995.

Paper III investigated whether individual variation in PIT effects was related to the balance between model-based and model-free control. Particularly, as PIT effects relate to the psychological and model-free/model-based speech to the computational dual-control framework of decision-making, this study provides insight on how both theoretical accounts relate to a common phenomenon.

Theoretical background As we have recently demonstrated in *Paper I* and *II* of this dissertation, human AD subjects show increased PIT effects but a reduction in model-based control. Moreover, animal studies have shown that individuals who show strong PIT effects and incentive salience attribution are insensitive to devaluation (Morrison et al., 2015), hence less goal-directed. However, the association between individual variation in PIT effects and the balance between model-free and model-based decision-making has yet not experimentally been tested in humans.

Hypotheses Based on the above mentioned animal findings and in line with our findings from *Paper I* and *II*, we expected that subjects with high PIT effects (Fig 1C) to show increased model-free but decreased model-based behavior in the Two-Step task (Fig 2A)

Major findings In line with what we expected, individuals with strong PIT effects relied less on model-based reinforcement learning. This pattern was evident in two independent samples and was confirmed by reaction time (RT) analyses and computational models. Contrary to several theoretical papers (Dolan and Dayan, 2013; Dayan and Berridge, 2014), we did not find evidence for an association between PIT effects and model-free control per se. This null effect is in line with our findings from *Paper II* and suggests that the Two-Step task does not have much power to detect variations in the model-free domain.

5.4 Paper IV

Nebe, S., Kroemer, N.B., Schad, D.J. Bernhardt, N., **Sebold, M.**, Mller, D.K., Scholl, L, Kuitunen-Paul, S., Heinz, A., Rapp M.A., Huys, Q.J.M, Smolka, M.N.(under Review at Addiction biology): No association of goal-directed and habitual control with alcohol consumption in young adults.

Based on our findings from *Paper II* that AD is associated with a reduction in model-based control, the major aim of *Paper IV* was to investigate whether this altered decision-making pattern was a preexisting trait that indexes alcohol consumption before chronic alcohol intake. As early alcohol use is a risk factor for adult AD (Grant et al., 2006; Hingson and Zha, 2009), we tested whether the imbalance between model-free and model-based control was associated with early alcohol consumption in a sample of healthy 18 year-old men.

Theoretical background Several animal studies have suggested that alterations in the decision-process predate the onset of addiction (Belin et al., 2008). Particularly, model-free at the expense of model-based decisions has been suggested to serve as a vulnerability marker for addiction development (Story et al., 2014; Keramati et al., 2012). On a neural level, activity of the ventral striatum (VS) and the medial prefrontal cortex (mPFC) modulate the balance between model-based and model-free control (Daw et al., 2011). So far, it has not been tested whether the balance between both systems and its neural correlates is associated with alcohol consumption before excessive alcohol intake.

Hypotheses We expected current alcohol consumption in young healthy adults to correlate with the balance between model-based and model-free control. More precisely, we hypothesized young subjects with increased alcohol intake to demonstrate a shift from model-based to model-free control. We further assumed that these behavioral alterations would be accompanied by increased model-free but decreased model-based neural signatures.

Major findings On a behavioral level, the balance between model-free and model-based decision-making was not associated with alcohol consumption. Furthermore, alcohol consumption was not related to neural correlates of model-free or model-based control in the VS or mPFC. Additional exploratory analyses revealed that early onset of drinking was associated with increased model-free signatures in the posterior putamen. These results suggest that an imbalance between model-based and model-free control might rather develop as a consequence of chronic alcohol intake than being a trait marker of alcohol intake per se.

6 Discussion

In the following chapter, I will summarize the findings of all studies and integrate them into existing knowledge and the debate about a shift from goal-directed to habitual control in AD.

6.1 Summary and Evaluation

6.1.1 AD patients show increased habits but reduced goal-directed control

Several animal studies have suggested that chronic alcohol consumption shifts behavioral control from goal-directed to habitual mode. It is yet unclear whether this relates to humans. In *Paper I* and *Paper II* we addressed this question by measuring habitual vs. goal-directed decision-making using two different paradigms. The paradigm we used in *Paper I* was strongly influenced by findings in animal studies, which indicate that chronic AD increases the extent to which Pavlovian cues exert control over a previously acquired instrumental response (PIT). In this dissertation, I argue that the PIT phenomenon relates to the psychological framework of habitual control. In *Paper II*, we used an experiment that enables the investigation of model-free and model-based decision-making - the computational instantiation of habitual and goal-directed control. Results from both papers partially confirm our hypothesis that AD is associated with a shift from goal-directed to habitual control.

Paper I: PIT Effects in AD

In *Paper I* we observed that compared to healthy controls, a proportional higher number of AD patients showed a significant PIT effect towards stimuli, which were associated with monetary outcomes. In a recent study of our group *(Paper V)*, we

extended these findings by showing that AD patients showed a more pronounced magnitude of those PIT effects. These findings are in accordance with animal studies, which show, that chronic alcohol intake increases value attribution to cues (Ostlund et al., 2014; Krank, 2003). The cues we used in *Paper I* and *Paper V* were associated with money rather than alcohol outcomes. However, several studies in animals have shown that chronic alcohol intake particularly increases the impact that alcohol cues exert on choice behavior. Therefore in *Paper I*, we additionally assessed the question whether AD was associated with increased PIT effects towards alcohol cues. In line with our results on PIT effects towards monetary cues, we found that alcohol-stimuli exerted stronger control over choice behavior in AD subjects compared to healthy controls. However, unlike monetary cues, alcohol cues appeared to suppress rather than enhance instrumental responding. In a recent paper of our group *(Paper VII)*, we replicated this finding. These results suggest that alcohol-cues in our PIT task might have been aversive to AD patients rather than appetitive, which contradicts with some findings and theories (Carter and Tiffany, 1999; Berridge, 2012). In patients, it is plausible that explicit alcohol cognitions instead of implicit value attributions to alcohol-cues inhibited responding. All patients had recently gone through detoxification. Interventions during detoxification typically target explicit alcohol cognitions, so they are ultimately negative. Therefore decreased responding towards alcohol cues in the here applied task might not reflect PIT effects, in the sense of implicit habits. Instead action selection in the patient group seemed to be under control of explicit cognitions, which is a hallmark of goal-directed control. If this was the case, suppression towards alcohol cues in patients would potentially reflect treatment effectiveness and therefore serve as a resilience factor for relapse. Indeed, in our recent study *(Paper VII)*, we observed that reduced responding in the presence of alcohol cues were particularly apparent in patients who successfully remained abstinent from alcohol during the follow-up period, while this was not the case in prospective relapsers.
Taken together, in *Paper I*, we were able to observe increased control of monetary-cues over instrumental behavior in AD. However, instrumental responding towards Pavlovian alcohol-cues may not reflect habitual but rather goal-directed responding in patients. The application of computational models that assume a hierarchical organization of habitual and goal-directed control might help to elucidate how both mechanisms interact in AD (Dezfouli and Balleine, 2013; Iglesias et al., 2013). Moreover, future studies should investigate non-treatment seeking AD patients in order to see whether goal-directed responding towards alcohol cues is only apparent after detoxification treatment.

Paper II: Model-free and Model-based decisions in AD

In *Paper II*, we approached the question about a shift from goal-directed to habitual control in AD from a computational perspective. In line with other studies that have tested this hypothesis with other tasks (Sjoerds et al., 2013; Ersche et al., 2016; McKim et al., 2016a), we demonstrated that AD is associated with a shift away from model-based decision strategies, the computational instantiation of goal-directed control. We did not evidence an increase in habitual, model-free behavior, which we had originally assumed. One recent study has suggested that the here applied Two-Step task does not have much power to detect variations in the model-free system (Doll et al., 2016). In line with this assumption, several other studies found that a variety of experimental manipulations would exclusively affect model-based control but not the model-free system in the Two-Step Task (Eppinger et al., 2013; Otto et al., 2013b; Worbe et al., 2015). In our study, disruptions in the model-based domain in patients were particularly apparent when subjects had to adapt their behavior after trials where no reward was delivered. This result is in line with other studies demonstrating that chronic alcohol intake reduces behavioral adaptation after negative outcomes (Ersche et al., 2016) and suggests that alcohol mainly impairs behavioral adaptation after punishment (Ridderinkhof et al., 2002; Lawrence et al., 2009).

Shortly after *Paper II* was published, another study used the Two-Step Task to investigate the shift between model-based and model-free control in methamphetamine dependent and AD subjects (Voon et al., 2015). Whereas this study found evidence of a disruption in model-based control in methamphetamine-dependent subjects, AD patients did not differ from healthy controls regarding model-free or model-based choice strategies. Because sample sizes between *Paper II* and Voon et al. (2015) were comparable, the null result in Voon et al. (2015) can not be attributed to reduced statistical power. Instead, differences in abstinence duration in the AD cohorts between *Paper II* and Voon et al. (2015) may have resulted in contradictory results: whereas AD patients in *Paper II* were abstinent for a maximum of 5 weeks, the maximal abstinence time in the Voon study was one year. Indeed, in the Voon study, weeks of abstinence were positively correlated with increases in model-based control, suggesting that impairments in model-based control might be a transient and acute consequence of chronic alcohol intake, which regularizes with prolonged abstinence.

6.1.2 Computational and psychological phenomena: Overlaps

In this thesis, I have argued that there are several phenomena, that characterize a shift from goal-directed to habitual decision mode. Essentially, I assume that some phenomena (PIT, incentive salience attribution, devaluation sensitivity) relate to the psychological dual-control framework whereas others (model-free/model-based control) are associated with the computational account and that both accounts reflect related phenomena. The paradigmatic overlap of various phenomena that capture the psychological account has been demonstrated: PIT effects predict resistance to outcome devaluation (Barker et al., 2014), incentive salience attribution is associated with enhanced PIT effects (Garofalo and di Pellegrino, 2015) and decreased devaluation sensitivity (Morrison et al., 2015). In *Paper III*, we addressed the yet unanswered question how PIT effects relate to the computational framework of model-free and model-based control. As stated in 6.1.1. AD patients show enhanced PIT effects and reductions in model-based control. In accordance with these findings, we demonstrate that healthy subjects who show strong PIT effects towards monetary cues also show less model-based control. This finding adds to two other studies, which use the here applied Two-Step Task and a devaluation task to demonstrate that the computational and the psychological dual control framework are related (Friedel et al., 2014; Gillan et al., 2015). Furthermore, our finding from *Paper III* suggests a common underlying substrate for Pavlovian interference and disruptions in model-based control.

6.1.3 Reductions in model-based control: a trait disposition to AD?

One important topic in the research on human AD is the unresolved causality dilemma, which is due to the correlative and cross-sectional nature of most human studies. Thus, it remains unclear whether the described shift from goal-directed to habitual decision-making in AD reflects a consequence of long-term drinking or a preexisting trait may serve as a vulnerability marker for AD. In order to address this question, the Lead study applies a longitudinal design and in *Paper IV* we have analyzed the first assessment cycle of a young healthy cohort of male subjects, who had started to consume alcohol just recently. As certain habitual decision-making phenotypes have been suggested to lead to early and numerous encounters with alcohol (Story et al., 2014; Montague et al., 2012), in *Paper IV* we aimed to test whether alcohol consumption in young adults was associated with a shift from model-based and model-free control. Some neuroimaging studies have shown that alcohol consumption in young adults is associated with increased neural responses in the striatum, which has been associated with habitual control (Dager et al., 2013; Brumback et al., 2015) and decreased activity in prefrontal areas associated with goal-directed control (Whelan et al., 2014; Squeglia et al., 2011). Therefore we had assumed that current and past alcohol intake in our sample of young adults would reflect these neural response pattern. However, we could not substantiate our behavioral nor our neural hypothesis. This finding is in line with a recent study where individual drinking pattern in a subclicical cohort were neither associated with habitual behavior, as indexed by individual PIT effects nor it's electrophysiological correlates (Martinovic et al., 2014). Furthermore our results of *Paper IV* suggest that the transition from goal-directed to habitual control, as seen in *Paper I* and *Paper II* occurs during later steps on the path to AD rather than being a preexisting trait marker for alcohol use.

6.2 Limitations

The here presented studies bear some limitations. First of all I will refer to conceptual and theoretical problems of the habit approach in SUD. Then, I will address the most significant methodological limitations of our studies and relate the conclusion of our findings to potential avenues for future research.

6.2.1 Habits in addiction: Conceptual and theoretical problems

There is accumulating evidence that addiction is not uniquely characterized by automatic actions, which are disentangled from the anticipatory effects of the action's consequences. Instead, some form of addictive behavior is truly goal-directed. This becomes particularly apparent in situations where SUD individuals apply complex sequences of actions in order to purchase the drug. Furthermore, it has been discussed, whether drug taking behavior which is preluded by subjective craving should be labeled as goal-directed actions, as drug taking then underlies it's motivational underpinnings (Sjoerds et al., 2014). On the other hand, craving in SUD has been suggested to reflect a rather automatic and reflexive response, that is stimulus bound - the hallmark of habitual control (Robinson and Berridge, 1993; Heinz et al., 2009). Thus, albeit drug purchase and consumption might be executed in a goal-directed manner, the initiation of these action sequences might still underly habitual responses. Indeed, there are several studies (including *Paper I*, in which we found that PIT responses towards alcohol cues in AD may be goal-directed rather than habitual), which suggest that goal-directed processes still play a major role in addiction (Root et al., 2009; Hogarth and Chase, 2011; Olmstead et al., 2001). One limitation of our studies is, that we did not investigate the above mentioned potentially goal-directed phenomena in addiction (namely: drug seeking and intake). Instead we examined general reward related instrumental choices. Whereas in animals, drug seeking is often experimentally induced and drug intake can be objectively quantified, in humans there are ethical limitations that restrict the experimental evocation of drug-related actions and craving and intake mostly rely on subjective reports of the patients. Thus, the tasks used in this dissertation and elsewhere in humans (Ersche et al., 2016; Voon et al., 2015; McKim et al., 2016b) use non-drug related rewards, whereas previous rodent studies that have shown a bias towards habitual control after chronic alcohol intake used alcohol rewards (Dickinson and Balleine, 2002; Lopez et al., 2014; Corbit et al., 2012). Moreover, human behavior is more complex than observed in laboratory rodent experiments, where animals are extensively trained. Thus, the translation from animal to human behavior (and vice versa) remains a crucial challenge and distinct findings between the two research subjectives should be treated with caution.

6.2.2 Methodological limitations

Our first methodological limitation refers to sample size restrictions. This problem particularly refers to *Paper I and II*, where we analyzed behavioral pilot data of the LeAD study and the results of both studies remain to be replicated in independent and larger samples. As for *Paper I*, we were able to replicate our finding, that reward-related monetary cues elicited increased approach responding *(Paper V)*, whereas alcohol cues elicited suppression of approach responding *(Paper VII)*. A more fundamental methodological limitation of *Paper I* is, that the PIT paradigm as applied here leads to a positive skewed distribution of individual PIT effects. Thus, many subjects did not show PIT effects at all, a finding we had not expected based on previous studies using a similar version of the paradigm (in Huys et al. (2011), 98% of all subjects showed a positive PIT effect). This skewed distribution limited our statistical approaches in *Paper I*. Moreover one limitation of *Paper I* was, that our experimental manipulation did not allow to disentangle between outcome-specific and outcome-general PIT (see 2.1.2). This was the case, because we had only one common outcome in the instrumental and the Pavlovian conditioning part, which was money. Recent studies in humans have introduced experimental manipulations that allow to disentangle both phenomena (Prévost et al., 2012; Lewis et al., 2013) and future studies should investigate both PIT versions in human SUD including AD.
Beside the sample size restrictions, a methodological limitation of *Paper II* was, that our finding of decreased model-based control in AD patients was confounded with decreased neuropsychological testing scores in the patient group. Indeed, when we controlled for interindividual differences in processing speed (digit symbol substitution test: DSST), our group differences in model-based control were no longer significant. We have recently shown that processing speed was associated with model-based control in healthy subjects *(Paper VI)*, a finding which has been replicated (Reiter et al.,

2016; Gillan et al., 2016). Deficits in the DSST test in AD patients are a common finding (Davies et al., 2005) and there is a wide debate on whether it is appropriate to control for substantive group differences on variables which are seen as features rather than confounds of the psychopathology (Miller and Chapman, 2001). Therefore, we do not think our results of decreased model-based control in AD are invalid. Instead our findings suggest that AD is associated with alterations in several, potentially associated cognitive subdomains, including model-based control and processing speed. One further limitation of Paper II relates to the experimental procedure, as one recent computational study demonstrated that model-based control in the Two Step Task does not improve accuracy. Therefore the application of additional cognitive capacity, which is needed in model-based decision-making might not pay off for the individual (Kool et al., 2016). These researchers have suggested an alternative task to solve this problem and future studies should apply this task to the clinical field.

In *Paper III*, where we associated individual PIT effects with model-based control, we analyzed data of two samples, which markedly differed regarding their demographic characteristics: The exploration sample contained middle aged healthy controls, the replication sample consisted of a homogeneous sample of 18 year old male subjects. We found a negative association between PIT effects and model-based control across both samples, although the association between both phenomena was stronger in the exploration sample. One limitation of *Paper III* was, that both samples markedly differed in their behavior across both tasks: Young subjects showed pronounced model-based control but low PIT effects, while older subjects particularly relied on model-free control in the Two-Step task and showed higher PIT effects. Whereas there is evidence that age reduces model-based control (Eppinger et al., 2013), there is to date no evidence that age increases PIT effects. Both samples might have differed in non demographic variables that we did not control for, such as stress or trait impulsivity, as assessed by the Barratt Impulsiveness Scale (Patton et al., 1995). Both of these variables were shown to enhance PIT effects but decrease model-based control (Morgado et al., 2012; Otto et al., 2013b; Deserno et al., 2015; Garofalo and di Pellegrino, 2015). Future studies can more specifically control for these potentially confounding effects. One second limitation of *Paper III* was that we followed a correlational approach where we associated individual behavior across two independent tasks rather than experimentally manipulating behavior within one task, as previously shown (Otto et al., 2013a; Gillan et al., 2015). Future studies should therefore additionally assess the influence that Pavlovian stimuli exert over model-based behavior.

All studies presented here applied a cross sectional design. At least in *Paper IV* this factor precludes us from reasoning that model-based disruptions do not reflect a predisposing vulnerability marker for increased alcohol intake. This conclusion can exclusively been drawn from longitudinal designs, e.g. by demonstrating that subjects show decreased model-based control after they had started to consume increased levels of alcohol, but showed no such alterations prior to alcohol intake. One of the overarching aims of the LeAD study is to apply these longitudinal approaches and will hopefully shed light on these unresolved chicken-egg problems.

6.3 Future Directions and Conclusions

6.3.1 Clinical implications

One important challenge of fundamental clinical studies is the translation into clinical practice. Our findings from *Paper I and II* have major clinical implications.
Study I demonstrated that behavior in AD patients after detoxification is likely to be controlled by reward predictive cues. This finding has twofold implications for psychotherapeutic interventions: First of all, the identification of healthy activities (physical exercise, performing music, create arts), that are experienced as rewarding but are non-alcohol related seems crucial. Cognitive appraisal (Connors et al., 1996) can help to increase the value of these healthy behaviors and decrease the value of undesired activities, such as alcohol consumption. Consequently, the repeated execution of healthy activities could establish PIT effects, such that environmental situations in which these behaviors are executed automatically promote them in the future. Second, the identification of environmental cues that are individually perceived as rewarding are important. Euthymic therapy (Lutz, 2005; Kiermeir et al., 2012) may help to further increase the value of these cues. Consequently, these environments could help to facilitate the execution of desired behavioral strategies. One example for this is, that listening to music might help to do physical exercise, which has been argued to prevent relapses (Lynch et al., 2013) as it reduces alcohol craving (Ussher et al., 2004).
Our finding from *Paper II* holds further promises for treatments for AD. As we evidenced disruptions in goal-directed decision-making in AD, psychotherapeutic interventions should include the exercise of goal-directed strategies. Indeed, this is part of cognitive behavioral therapy, as in the S-O-R-C model (Kanfer and Saslow, 1965), where the affected individuals learn to actively store and retrieve a mental model on how they should alternatively react to craving inducing stimuli.

6.3.2 Conclusion

In conclusion, this thesis demonstrates that AD is associated with several habit-related phenomena, such as increased PIT effects and reductions in model-based control. Moreover, in a healthy cohort these phenomena were associated with each other (in the way that subjects with high PIT effects showed low model-based control), suggesting that they involve similar cognitive mechanisms. Future studies should use neuroimaging and electrophysiological techniques along with these paradigms to further elucidate the precise mechanism that are altered in AD and to further clinical treatment strategies. Moreover, longitudinal studies involving at risk populations, as well as non-abstinent AD subjects are needed to answer the question whether habitual decision-making relates to a trait marker of AD or a transient state marker tracking clinical fluctuations over time.

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